Remarks

Claims 1-20 are pending in the application. Claim 1 has been amended to more particularly point out and claim the invention. No new matter has been added.

Rejections under 35 USC 103

Claims 1, 5, 7, and 19 are rejected as unpatentable over Jiro, et al. JPH3[1991]-47097 (February 28, 1991)("Jiro") in view of Gelfi et al., (Biotechniques 21: 926-32, 1996) ("Gelfi"), and further in view of Carreira et al., Anal. Biochem. 106:455-68, 1980 ("Carreira"). The rejection is traversed to the extent it is applied to claim 1 as amended, and as applied to the remaining claims.

Claim 1, from which depends claims 5 and 7, is drawn to a method that requires, *inter alia*, subjecting an electrophoretic medium to an electric field to result in the electrophoretic migration of one, or more, target molecules into at least one region of the electrophoretic medium containing immobilized capture probes (step b), then dissociating the targets and their complementary capture probes (step c), and then applying an electric field while maintaining the dissociating conditions within the electrophoretic medium, thereby causing the dissociated target molecules to exit the electrophoretic medium by electrophoretic migration (step d). The last recited step specifies collecting the dissociated target molecules that have exited the electrophoretic medium (step e). Claim 19 similarly requires in steps b-e the electrophoretic migration of target molecules into immobilized capture probes, after which the target molecules and their capture probes are dissociated, subjected to an electric field and collected.

The cited references cannot be properly combined to render the claimed invention *prima facie* obvious because modifying Jiro with the teachings of Gelfi and Carreira would make the

method of Jiro unusable for its intended purpose. The Federal Circuit has stated that if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

In the present Office Action, the Examiner acknowledges that Jiro does not teach a step of imposing conditions on the electrophoretic medium that dissociates the targets and their complementary target probes. To overcome this deficiency, the Examiner turns to Gelfi and Carreira. According to the examiner, the artisan would use Gelfi's method of increasing a thermal gradient to cause denaturation of hybridization complexes.

However, a completely denaturing hybridization as taught by Gelfi would render Jiro's method unworkable. In Jiro, a nucleic acid target molecule is electrophoresed into capture probes immobilized in the electrophoretic medium (see, e.g., page 6, first full paragraph). Jiro further teaches that the hybridized target molecule is detected using a labeled second nucleic acid probe, which hybridizes to a region of the hybridized target molecule (see page 6, second full paragraph). Detection of the label reveals the existence of the hybridized target molecule. An example of a labeled second nucleic acid probe is provided in Embodiment 1 at page 9.

Thus, the method of Jiro is dependent on the formation and detection of two separate regions of complementarity in three nucleic acids: the hybridization that occurs between a capture probe and a target molecule, and the hybridization that occurs between the target molecule and a labeled second nucleic acid probe. Subjecting this complex to the dissociating conditions taught by Gelfi would make it impossible to detect a target molecule that had bound to a capture probe.

The present rejection is thus analogous to the issue presented to the Federal Circuit in *Gordon.* The invention in dispute in that case was a blood filter assembly for use during medical procedures wherein both the inlet and outlet for the blood were located at the bottom end of the

filter assembly, and wherein a gas vent was present at the top of the filter assembly. The prior art reference taught a liquid strainer for removing dirt and water from gasoline and other light oils wherein the inlet and outlet were at the top of the device, and wherein a pet-cock (stopcock) was located at the bottom of the device for periodically removing the collected dirt and water. The reference further taught that the separation is assisted by gravity. The Federal Circuit concluded the invention was non-obvious, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose, because the gasoline to be filtered would be trapped at the top, the water and heavier oils sought to be separated would flow out of the outlet instead of the purified gasoline, and the screen would become clogged.

Similarly, dissociating annealed nucleic acids as taught by Gelfi would render the method and electrophoretic system of Jiro inoperative, because it would not be possible to detect target molecules that had bound to immobilized capture probes.

A second reason the combination of references cannot be used is that modifying Jiro by combining with Gelfi changes the principle of operation of the method of Jiro. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). In *Ratti,* the claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. The patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a

substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

Combining Gelfi with Jiro would similarly require a substantial reconstruction and design of the method described in Jiro. Dissociating bound nucleic acids as taught in Gelfi destroy the ability to detect *in situ* target molecules that had bound to immobilized capture probes. Even if target molecules were detectable, they would have to be detected in a manner that would change the principle of the method described in Jiro. Therefore, Gelfi cannot be combined with Jiro to render obvious the invention of claims 1, 5, 7, and 19.

The last remaining reference, Carreira, is cited only for describing a method of collecting purified target molecules that have exited an electrophoretic medium. It has no teaching or suggestion that overcomes the non-combinability of Jiro and Gelfi with respect to the claimed invention. Thus, Applicants submit that the invention of claims 1, 5, 7 and 19 is non-obvious over the combination of Jiro, Gelfi, and Carreira.

Claims 2-4, 10-14, and 16 are rejected as unpatentable over Jiro in view of Gelfi, further in view of Carreira, and further in view of Cantor, US Patent No. 5,482,836 ("Cantor"). The rejection is traversed.

Claims 2-4 depend from claim 1. Claim 10, from which depends claims 11-14, and 16, includes steps that correspond to steps (b)-(e) of claim 1 and claim 19. For the reasons explained above, Jiro, Gelfi, and Carreira are not combinable to produce the invention of claim 1. Nor are these references properly combinable with Cantor to produce a method that includes steps (b)-(e) as recited in claim 10. Cantor is cited for describing a multiplex assay that uses microtiter plates; however, this reference has no teaching or suggestion that overcomes the non-combinability of Jiro and Gelfi with respect to the claimed invention. Therefore, claims 2-4, 10-

14, and 16 are non-obvious over the combination of Jiro, Gelfi, Carreira, and Cantor.

Claims 8, 9, 17 and 18 are rejected as unpatentable over Jiro in view of Gelfi, further in view of Carreira, further in view of Cantor, and further in view of Mullis, US Patent No. 4,683,202 ("Mullis"). Applicants traverse.

Claims 8 and 9 depend from claim 1, and claims 17 and 18 depend from claim 10. As discussed above, Jiro, Gelfi, and Carreira are not combinable to produce the invention of claim 1. Nor are they combinable with Cantor to produce a method that includes steps (b)-(e) as recited in claim 10. While Mullis is cited for describing a method using extension of primers to form complementary primer extension products that act as templates for synthesizing a desired nucleic acid sequence, this reference lacks any teaching that overcomes the deficiencies of Jiro, Gelfi, Carreira and Cantor with respect to making obvious the claimed invention. Therefore, claims 8, 9, 17 and 18 are non-obvious over the cited references.

Claims 6 and 15 are rejected as obvious over Jiro in view of Gelfi, further in view of Carreira, and further in view of Stamato et al., US Patent No. 4,830,726 ("Stamato"). The rejection is traversed.

Claim 6 depends from claim 1, and claim 15 depends from claim 10. The combination of Jiro, Gelfi, and Carreira cannot be used to make obvious the invention of claims 1 and 10. Stamato, which is cited for describing a method of separating DNA molecules by gel electrophoresis that employs alternate applications of high and low strength electric fields in opposite directions, has no teaching or suggestion that overcomes the deficiencies of Jiro, Gelfi, and Carreira with respect to the claimed invention. Thus, claims 6 and 15 are non-obvious over the cited references.

Claim 20 is rejected as unpatentable over Jiro in view of Gelfi, further in view of Carreira,

and further in view of Ghosh et al., US Patent No. 5,478,893 ("Ghosh"). The rejection is traversed.

Claim 20 depends from claim 19. Applicants have explained above that claim 19 is non-obvious over the combination of Jiro, Gelfi, and Carreira. Ghosh is cited for describing a method where capture probes are immobilized in an electrophoretic medium by copolymerizing a 5' acrylamide moiety with an electrophoretic medium. However, this reference lacks any teaching or suggestion that overcomes the deficiencies of Jiro, Gelfi, and Carreira with respect to the claimed invention. Therefore, claim 20 is non-obvious over the cited references.

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below. A petition for extension of time and revocation/new power of attorney accompany this response. The Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311, Reference No. 26597-562 CIPCON.

Respectfully submitted,

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